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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER
HOWARD, ZACHARY C

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,763	NAKAO ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,16 and 18-23* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13,15,16,22 and 23* is/are rejected.

7)☒ Claim(s) *11 and 22* is/are objected to.

8)☒ Claim(s) *1-13,15,16 and 18-23* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/25/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 1/22/10 has been entered in full. Claims 11, 13, 15, 16 and 22 are amended. Claims 14 and 17 are canceled. New claim 23 is added.

Claims 1-13, 15, 16 and 18-23 are pending in the instant application.

Claims 1-10 and 18-21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/8/09.

Claims 11-13, 15, 16, 22 and 23 are under consideration, in so far as they are drawn to the elected species.

Information Disclosure Statement

The Information Disclosure Statement of 11/25/09 has been considered.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (7/24/09).

The objections to the specification at pg 4 are *withdrawn* in view of Applicants' amendments to the specification.

All objections and/or rejections of claims 14 and 17 are moot in view of Applicants' cancellation of these claims.

The objection to claims 11, 15, 16 and 22 at pg 4 are *withdrawn in part* in view of Applicants' amendments to the claims. Specifically, grounds (1), (2), (4) and (5) at pg 4 are withdrawn in view of Applicants' amendments to the claims (ground (6) is moot in view of the cancellation of claim 17). However, the objection to claim 11 set forth in ground (3) is maintained for the reasons set forth below.

The rejection of claims 11-13, 15, 16 and 22 under 35 U.S.C § 112, second paragraph, at pg 5-6 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants'

amendments to the claims. However, please see the new rejection under 35 U.S.C. 112, 2nd paragraph necessitated by said amendments.

The rejection of claims 11-13, 15, 16, 22 under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter is *withdrawn* in view of Applicants' amendments to the claims.

The rejections of claims 11-13, 15, 16, 22 under 35 U.S.C. § 102(b) as being anticipated by Miyazawa et al (2002) are *withdrawn* in view of Applicants' amendment to independent claims 11 and 22 to limit the claims to systemically administering CNP or a derivative thereof. However, please see below a new rejection under 35 U.S.C. 103(a) necessitated by said amendments.

Maintained Objections and/or Rejections

Claim Objections

Claims 11 is objected to because of the following informalities:

Claim 11 uses an indefinite article ("a") with a definite characteristic (i.e., "a body height of an individual" should be "the body height of an individual"). Appropriate correction is required.

This objection was set forth at pg 4 of the 7/24/09 Office Action as ground (3) of the objections. Applicants' response filed on 1/22/10 states at pg 9 that "the instant claim amendments obviate the rejections listed in items (1) to (5) on page 4 ..." However, in the claims filed on 1/22/10, the indefinite article is retained in claim 11 (see line 1). Therefore, this objection is maintained.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-13, 15, 16, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method for increasing the body height of an individual free from fibroblast growth factor receptor 3 (FGFR3) abnormality, and wherein said individual has growth cartilage layers, comprising administering systemically a mammalian or avian C-type natriuretic peptide (CNP) or a derivative that has a deletion, substitution, or addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2 and wherein said derivative possess the ability to bind to G-CB and increase intracellular production of cGMP,

does not reasonably provide enablement for a method as recited in claims 11-13, 15, 16, 22 and 23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection was set forth at pg 6-12 of the 7/24/09 Office Action for claims 11-13, 15, 16 and 22; new claim 23 is herewith added.

Applicants' arguments (1/22/10; pg 10-12) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated, Applicants argue that the "claims are amended in an effort to expedite prosecution" (pg 11) and describe the independent claims as amended (pg 11-12). Applicants argue that the specification enables the amended claims (pg 12). Applicants argue that the amended claims "specify that the individual to whom CNP or a derivative thereof is administered has growth cartilage layers, i.e., the individual is not a post-puberty individual" (pg 12). Applicants further argue that in the working examples CNP was expressed systemically, and resulted in "the total thickness of the growth cartilage layers in mice with growth cartilage layers is significantly greater in terms of total thickness in comparison to wild type, which results in an increase in body height, see Example 6, Figure 5" (pg 12). Applicants further argue that the amended claims are limited to CNP or derivatives thereof "described in Japanese Patent Publication NO. 6-9688 (1994) and International Publication No. WO 02/074234" and that "an ordinary artisan would have recognized at the time of the invention, that the CNP derivatives in the instant claims would have an effect on GC-B activation". Applicants argue that "an ordinary artisan would have been able to identify activators of GC-B without undue experimentation" using "an assay system" described on pg 14 of the specification.

Applicants' arguments have been fully considered, and are found persuasive in part but the rejection is maintained. Specifically, it is found persuasive that the limitation "wherein the individual has growth cartilage layers" limits the method to growing individuals, thus excluding adults (post-puberty) individuals from the claims (practicing the claimed method with adults was held to lack enablement for the reasons set forth at pg 8-9 of the 7/24/09 Office Action). Thus, this basis of the rejection is withdrawn. Furthermore, it is found persuasive that the specification provides enablement for the claims as practiced with the new limitation of systemically administering CNP to growing individuals. It is also found persuasive that the amended claims have been narrowed such they no longer are directed to any form of "activating GC-B" (which encompassed administration of an activator of GC-B of any structure).

However, it is maintained that the claims encompass any "derivative" of CNP. The rejection set forth previously indicated the claimed method was enabled for "a CNP of SEQ ID NO: 1 or 2, a mammalian or avian C-type natriuretic peptide (CNP), or a derivative that has a deletion, substitution or addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2 wherein said derivative possesses the ability to bind to G-CB and increase intracellular production of cGMP". The claims have been amended to recite "C-type natriuretic peptide (CNP)" or a derivative thereof, where the derivatives are those specified in the claims. However, the term "C-type natriuretic peptide (CNP)" is not defined in the instant specification and is broader in scope than either "a CNP of SEQ ID NO: 1 or 2" or "a mammalian or avian C-type natriuretic peptide" (which would be limited to naturally-occurring mammalian or avian peptide). Instead, in absence of a limiting definition in the specification, and in view of the large number of derivatives of CNP described in the specification, the term "C-type natriuretic peptide (CNP)" broadly encompasses "a derivative" of CNP. Therefore, the rejection is maintained for the reasons of record set forth previously for the recitation of "CNP or a derivative thereof".

However, even if the claims were limited to derivatives as recited in lines 6-25 of claim 11 or lines 5-24 of claim 22, the claims would still lack enablement for the following reasons. These derivatives are not taught in the instant specification for the

reasons set forth in the section titled "Claim Rejections - 35 U.S.C. 112, 1st paragraph, new matter" (see below). It is acknowledged that the '133 patent teaches that "the present inventors unraveled the minimum activity structure which was necessary for the development of the aforementioned [strong cGMP producing] activity of CNP" (col 4, lines 13-17), and claims said structure in claim 1. Furthermore, as acknowledged previously (pg 11 of the 7/24/09 Office Action), in view of the teachings of the '234 publication the skilled artisan could practice the claimed methods with a CNP of SEQ ID NO: 1 or 2, a mammalian or avian C-type natriuretic peptide (CNP), or a derivative that has a deletion, substitution, or addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2 wherein said derivative possesses the ability to bind to G-CB and increase intracellular production of cGMP. However, the claims as amended are not directed to either genus. Instead the claims present a broader genus of derivatives that combines features of each. As described below, the "peptide sequence" of the claims does not match the sequence disclosed the '133 patent; instead, positions (I) and (J) include several additional amino acid substitutions. Even more significantly, the claims combine the deletions, substitutions, or additions of 1 to 10 amino acids in the sequence of CNP with the limitation of "possessing a CNP activity" (which could be any activity, rather than just cGMP production), and with the limitation of the "peptide sequence" recited in lines 6-25 of claim 11 or lines 5-24 of claim 22.

For these reasons it is maintained that the skilled artisan would not know which of the recited derivatives would retain activity necessary for use in the claimed method of increasing body height. The skilled artisan could make and test variants for cGMP production in an assay (such as disclosed at pg 14 of the specification), but this would require undue experimentation in view of (1) the essentially limitless number of mutations encompassed by the claims and (2) the evidence provided by Table 3 of '234 publication that many mutations, even single substitutions, in the CNP sequence result in a loss of activity. Furthermore, by broadening the "activity" to activities other than cGMP production, the specification merely invites the skilled artisan to test the derivatives for other activities even in they lack the activity of cGMP production.

Due to the large quantity of experimentation necessary to use the full scope of the variants of CNP encompassed by the claimed methods, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the invention of the claims with respect to the full scope of CNP derivatives encompassed by the claims.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 11-13, 15, 16, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 12-15 of the 7/24/09 Office Action for claims 11-13, 15, 16 and 22; new claim 23 is herewith added.

Applicants' arguments (1/22/10; pg 13) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that "GC-B activators described in the amended claims are limited to CNP or derivatives as disclosed in Japanese Patent Publication NO. 6-9688 (1994) and International Publication No. WO 02/074234" (pg 13) and therefore, "the CNP derivative described in the instant claims were known to activate GC-B" (pg 13).

Applicants' arguments have been fully considered but are not found persuasive. As described above in the section titled "Claim Rejections - 35 U.S.C. 112, 1st Paragraph, enablement", the claims still encompass any derivative of CNP. Furthermore, the claims as amended are not directed to a genus described in either the '133 patent or the '234 publication. Instead the claims present a genus of derivatives that is broader in that it combines features of each. As noted below, the "peptide sequence" of the claims does not even match the sequence of the '133 patent; instead, positions (I) and (J) include several additional amino acid substitutions. Even more

significantly, the claims combine the deletion, substitutions, or additions of 1 to 10 amino acids in the sequence of CNP, with the limitation of "possessing a CNP activity" (which could be any activity, rather than just cGMP production), with the limitation of the "peptide sequence" recited in lines 6-25 of claim 11 or lines 5-24 of claim 22.

For this reason, it is maintained that the specification fails to provide a written description of a genus of derivatives of CNP that can be used in the claimed method for increasing body height.

Therefore, a method for increasing the body height of an individual free from fibroblast growth factor receptor 3 (FGFR3) abnormality, and wherein said individual has growth cartilage layers, comprising administering systemically a mammalian or avian C-type natriuretic peptide (CNP) or a derivative that has a deletion, substitution, or addition of between 1 to 10 amino acids in the amino acid sequence of SEQ ID NO: 1 or 2 and wherein said derivative possess the ability to bind to G-CB and increase intracellular production of cGMP, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

New objections and/or rejections necessitated by Applicants' amendment

Specification

The disclosure is objected to because of the following informalities:

In the response filed on 1/22/10, Applicants have amended the specification at paragraph 3 on page 12 to recite ".....and International Publication No. WO 02/074234, which corresponds to U.S. Patent No. 5,434,133..." However, there is no apparent correspondence between '234 publication and the '133 patent. The '234 publication (cited on the 7/24/09 PTO-892) was published 9/26/02, claims priority no earlier than 2001, and has the inventors Golembo and Yayon, whereas the '133 patent was published 1/18/95 and has five different inventors (Tanaka et al).

According to Applicants' comments at page 8 of the response, it appears that Applicants instead meant to amend to assert a "correspondence" between Japanese

Patent Publication No. 6-9688A and U.S. Patent No. 5,434,133. However, even if the specification is amended to indicate such, the change will be objected to as Applicants have provided no evidence of a "correspondence" between the two publications.

Appropriate correction is required.

Claim Objections

Claims 11 and 22 are objected to because of the following informalities:

(1) In claim 11, line 2, there is an unnecessary comma between "fibroblast growth factor receptor 3" and "(FGFR3)".

(2) In claim 11, line 21, the word "Ala" is followed by a period instead of a comma.

(3) In claim 22, the abbreviation "CNP" should be accompanied by the corresponding full name (C-type natriuretic peptide).

(4) In claim 22, line 20, the word "Ala" is followed by a period instead of a comma.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-13, 15, 16, 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In each of claims 11 and 22, the terms "H-" and "-OH" are unclear.

(1) It is unclear whether the "H-" at position (A) refers to:

(a) a hydrogen atom (H-) of the free -NH_2 group at the N-terminus of the peptide;

(b) protonation of the N-terminal amino acid (addition of a proton, H^+); or

(c) a different amino acid modification (e.g. H-Cys could refer to homocysteine, or H-Ser could refer to hydroxyserine).

It is further unclear how (A) can be "H-" when (B) is always "H-Cys", as this would indicate that the cysteine is twice modified by "H-".

(2) It is unclear whether the "-OH" at position (K) refers to:

(a) the hydroxyl group (-OH) of the free –COOH group at the C-terminus of the peptide; or

(b) hydroxylation of the C-terminal amino acid (addition of hydroxyl anion, OH^-).

Claims 15 and 16 each recite the limitation “the CNP” in line 1. The antecedent basis for this limitation in each claim is unclear. Specifically, parent claim 11 now refers to CNP in line 3, but also refers to CNP (twice) in line 7. It is unclear which use is being limited by claim 15 or by claim 16. For purposes of prosecution, claims 15 and 16 are interpreted to broadly to be directed to each possibility. Thus, claims 15 and 16 are interpreted to encompass both the CNP of line 3 of claim 11 and also the derivatives of CNP of claim 11 starting on line 6.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 11-13, 15, 16, 22 and 23 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter. The claims contain new matter for the following reasons.

(1) Independent claim 11 has been amended to recite derivatives comprising "the following peptide sequence" that begins on line 9 of the claim. Independent claim 22 has been amended similarly. Applicants indicate that said derivatives are supported by pages 12-13 of the specification, which "teaches that the derivatives are described in Japanese Patent Publication No. 6-9688A (1994), which corresponds to U.S. Patent No. 5,434,133, and International Publication No. WO 02/074234".

As noted previously at pg 11 of the 7/24/09 Office Action, "Japanese Patent Publication NO. 6-9688A (1994)" does not appear on an IDS, and the Examiner has not been able to locate a JPO document with this number. Applicants have not submitted this document with the current response to provide evidence that it "corresponds" to

U.S. Patent NO. 5,434,133. Furthermore, none of the Patent Documents or Publications on the face of the '133 patent refer to a 6-9688A document. Thus, there is no evidence of record that the 6-9688A publication referenced in the specification contains disclosure identical to the '133 document, such that the '133 document could be used to support the incorporation of the newly claimed derivatives. In order to show support for the claimed subject matter in the 6-9688A publication, Applicants must provide a copy of this reference, including English translation as necessary, showing specific support for the claimed derivatives.

Furthermore, the '234 publication also does not disclose the peptide sequence beginning on line 9 of claim 11 or line 8 of claim 22.

Therefore, the peptide sequence beginning on line 9 of claim 11, and line 8 of claim 22, is not supported by the specification as originally filed and represents new matter.

Claims 12-13, 15, 16 and 23 each depend from claim 11 and encompass the same new matter. As set forth above in the section titled, "Claim Rejections - 35 USC 112, 2nd paragraph", claims 15 and 16 have each been interpreted as encompassing the derivatives of claim 11.

(2) Even if the '133 patent contains exactly the same disclosure as the 6-9688A publication, the claimed derivatives differ from those disclosed in the '133 patent.

(a) The derivatives shown in the '133 patent contains "Ser" and "Gly" in the positions indicated as "(I)" and "(J)" in claim 11, line 10 and claim 22, line 9, whereas the derivatives recited in the claims indicate that (I) is Gly, Lys, Ala or Leu, and (J) is Leu or Met.

(b) The derivatives of Claims 11 and 22 are not limited to "the following peptide sequence" but instead are more broadly directed to a genus of derivatives that both

"comprises a deletion, substitution or addition of between 1 to 10 amino acids in the amino acid sequence of CNP, while possessing a CNP activity" and

"comprises the following peptide sequence" (as shown, e.g., lines 8-24 of claim 11).

The derivatives of the '133 patent do not include these two limitations in combination. Specifically, the '133 patent does not teach that the derivatives further comprise a deletion, substitution or addition of between 1 to 10 amino acids in the amino acid sequence of CNP. Furthermore, the paragraph of the instant application referring to the 6-9688A publication, paragraph 61, only refers to derivatives disclosed therein, and does not further teach that they have the additional limitation of further comprise a deletion, substitution or addition of between 1 to 10 amino acids in the amino acid sequence of CNP.

The '234 publication also does not disclose (a) or (b) above.

Therefore, the derivatives beginning on line 6 of claim 11, and line 5 of claim 22, are not supported by the specification as originally filed and represent new matter.

Claims 12-13, 15, 16 and 23 each depend from claim 11 and encompass the same new matter. As set forth above in the section titled, "Claim Rejections - 35 USC 112, 2nd paragraph", claims 15 and 16 have each been interpreted as encompassing the derivatives of claim 11.

(3) New claim 23 teaches, "[t]he method of claim 11, wherein the individual is a patient with short stature disease". The only occurrence of "short stature disease" is on page 1, first paragraph (section "Technical Field") which teaches that "the composition of the present invention can be used for … or for increasing the body height in an individual **other than patients with short stature disease**" (emphasis added). The 1/22/10 response indicates that support for the new claim is found on page 8, second paragraph. However, this paragraph uses the term "short stature" but not "short stature disease". This paragraph does not define a genus that constitutes a "short stature disease". Instead, this paragraph describes "short stature free from FGFR3 abnormality" including "short stature caused by endocrine abnormalities", "short stature caused by non-endocrine abnormalities" and "secondary short stature caused by chemotherapy or radiation therapy". These teachings do not provide support for treatment of a genus described as "short stature disease".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-13, 15, 16, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazawa et al (2002. Endocrinology. 143(9): 3604-3610; cited previously), and further in view of Suda et al, 1998 (Proc Natl Acad Sci USA; reference CA on the 11/25/09 IDS).

The recitations of "for increasing a body height of an individual free from FGFR3 abnormality" and "to increase the body height in the individual" in the preamble of claim 11 are interpreted as an intended use and bear no accorded patentable weight to distinguish the claimed method over one from the prior art, except in so far as they limit the method to a particular patient population (an individual free from FGR3 abnormality). Furthermore, the instant specification defines a "FGFR3 abnormality" as referring to achondrogenesis or achondroplasia caused by growth inhibition of cartilage bones resulting from mutations in the FGRF3 gene; thus an "individual free from FGRF3 abnormality" includes any individual without a mutation in FGRF3. Therefore, claim 11 encompasses a method comprising administering systemically C-type natriuretic peptide (CNP) in an individual without a FGRF3 mutation and with growth cartilage layers.

Miyazawa et al teach a transgenic mouse that overexpresses CNP in a wildtype background (pg 3605). The mouse was generated by "targeted expression of CNP in the growth plate chondrocytes under control of the mouse pro-α1 (II) collagen (Col2a1) promoter. These mice do not have a mutation in the FGFR3 gene and have growth cartilage layers. Therefore, Miyazawa et al teach a method comprising administering systemically C-type natriuretic peptide (CNP) in an individual without a FGRF3 mutation and with growth cartilage layers.

Miyazawa et al do not teach systemic administration of CNP.

Suda et al teach generation of BNP-transgenic mice under the control of the human serum amyloid P component promoter (pg 2337). Suda et al further teach "We report here marked skeletal overgrowth in transgenic mice that overexpress BNP. Transgenic mice with elevated plasma BNP concentrations exhibited deformed bony skeletons characterized by kyphosis, elongated limbs and paws, and crooked tails" (see Abstract). Suda et al further teach "In the present study, we also observed that CNP, a selective activator of GC-B, increases the total longitudinal bone growth and cGMP production in cultured embryonic mouse tibias more potently than BNP, an activator of GC-A. These findings suggest strongly that activation of chondrogenesis by natriuretic peptides is mediate primarily by GC-B. Because BNP is overproduced specifically by the liver and not in the bone from BNP-transgenic mice, we postulate that BNP secreted into the circulation in a large quantity cross-reacts with GC-B in the growth plate chondrocytes, thereby causing skeletal overgrowth of vertebrae and long bones in these animals ... It is tempting, therefore, to speculate that CNP is the endogenous ligand for GC-B in the bone in vivo and is involved in the process of endochondral ossification" (pg 2341).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the human serum amyloid-P component promoter used by Suda et al for the mouse pro-α1 (II) collagen (Col2a1) promoter in the CNP-transgenic mice taught by Miyazawa, thus creating a CNP-transgenic mice wherein CNP is expressed in the plasma rather than locally in collagen. The person of ordinary skill in the art would have been motivated to do so because Suda et al teaches CNP

promotes a greater growth in *in vitro* experiments, suggesting that CNP is the actual ligand for GC-B in the bone. The skilled artisan would have had a reasonable expectation of success in creating said transgenic mice because it would simply require creating CNP transgenic mice as previously described, but with a simple substitution of one promoter known in the art for local expression for another known in the art for systemic expression. The skilled artisan would have had a reasonable expectation of success in using CNP systemically because of the success of Suda et al in using BNP systemically.

Claims 12 and 13 each encompass a method of claim 11 wherein the increase in body height is due to an extension of cartilage bones that are tibiae. Thus, each dependent claim solely limits the intended use of claim 11, and is therefore unpatentable over Miyazawa et al in view of Suda et al for the same reasons as for claim 11 described above.

As amended, claim 15 depends from claim 11 and limits the CNP to CNP-22 or CNP53 from mammals. CNP-53 is a precursor of the CNP-22 peptide. Thus, the transgenic mice taught by Miyazawa et al would produce both CNP-53 and CNP-22. Therefore, claim 15 is unpatentable over Miyazawa et al in view of Suda et al for the same reasons as for claim 11 described above.

As amended, claim 16 depends from claim 11 and recites that the CNP is the CNP-22 of SEQ ID NO: 1 or CNP-53 of SEQ ID NO: 2. SEQ ID NO: 1 and 2 are disclosed as human sequences in the instant Sequence Listing. However, mouse CNP-22 sequence is inherently identical to the human CNP-22 sequence of SEQ ID NO: 1 ("[m]olecular cloning of the CNP precursor in the pig, rat, human and mouse has revealed that the primary structure of CNP-22 is identical in these species"; pg 331 of Komatsu et al, 2002. J Bone Miner Metab. 20: 331-336; cited previously solely to provide evidence of inherency). Therefore, claim 16 is unpatentable over Miyazawa et al in view of Suda et al for the same reasons as for claim 11 described above.

Claim 22 is an independent claim; the recitation of "for extending a cartilage bone free from FGFR3 abnormality in an individual" in the preamble of claim 22 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed

method over one from the prior art. Therefore, as amended claim 22 encompasses a method comprising administering systemically CNP to activate guanyl cyclase B (GC-B) in an individual with bones free from FGFR3 abnormality, and wherein the individual has growth cartilage layers. Claim 22 is unpatentable over Miyazawa et al in view of Suda et al for the same reasons as for claim 11 described above.

New claim 23 depends from claim 11, and limits the individual to a patient with "short stature disease". The term "short stature disease" is not defined in the specification, and is interpreted broadly to encompass any patient with a condition resulting lessened growth. Miyazawa et al further teach CNP-deficient mice that exhibit dwarfism as a result of impaired endochondral ossification, and that targeted (local) expression of CNP in the growth plate chondrocytes rescued the growth of these mice (pg 3604). It would have been further obvious to take CNP-deficient mice and express CNP in them, but substitute the human serum amyloid-P component promoter used by Suda et al for the mouse pro-α1 (II) collagen (Col2a1) promoter in the CNP-transgenic mice taught by Miyazawa, thus creating a CNP-transgenic mice wherein CNP is expressed in the plasma rather than locally in collagen. The skilled artisan would have been motivated to determine if plasma-based expression of CNP could also rescue the growth defect of the CNP-deficient mice. The skilled artisan would have had a reasonable expectation of success in creating said transgenic mice because it would simply require creating transgenic mice as previously described, but with a simple substitution of one promoter known in the art for local expression for another known in the art for systemic expression. The skilled artisan would have had a reasonable expectation of success in using CNP systemically because of the success of Suda et al in using BNP systemically.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647